Multivariate meta-analyses of mitochondrial complex I and IV in major depressive disorder, bipolar disorder, schizophrenia, Alzheimer disease, and Parkinson disease

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Abstract: Complex I (NADH dehydrogenase, NDU) and complex IV (cytochrome-c-oxidase, COX) of the mitochondrial electron transport chain have been implicated in the pathophysiology of major psychiatric disorders, such as major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ), as well as in neurodegenerative disorders, such as Alzheimer disease (AD) and Parkinson disease (PD). We conducted meta-analyses comparing complex I and IV in each disorder MDD, BD, SZ, AD, and PD, as well as in normal aging. The electronic databases Pubmed, EMBASE, CENTRAL, and Google Scholar, were searched for studies published between 1980 and 2018. Of 2049 screened studies, 125 articles were eligible for the meta-analyses. Complex I and IV were assessed in peripheral blood, muscle biopsy, or postmortem brain at the level of enzyme activity or subunits. Separate meta-analyses of mood disorder studies, MDD and BD, revealed moderate effect sizes for similar abnormality patterns in the expression of complex I with SZ in frontal cortex, cerebellum and striatum, whereas evidence for complex IV alterations was low. By contrast, the neurodegenerative disorders, AD and PD, showed strong effect sizes for shared deficits in complex I and IV, such as in peripheral blood, frontal cortex, cerebellum, and substantia nigra. Beyond the diseased state, there was an age-related robust decline in both complexes I and IV. In summary, the strongest support for a role for complex I and/or IV deficits, is in the pathophysiology of PD and AD, and evidence is less robust for MDD, BD, or SZ.

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Running title: Meta-analyses of mitochondrial complex I and IV

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Abstract

Complex I (NADH dehydrogenase, NDU) and complex IV (cytochrome-c-oxidase, COX) of the mitochondrial electron transport chain have been implicated in the pathophysiology of major psychiatric disorders such as major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SZ), as well as in neurodegenerative disorders, such as Alzheimer disease (AD) and Parkinson disease (PD).

We conducted meta-analyses comparing complex I and IV in each disorder MDD, BD, SZ, AD PD, as well as in normal aging. The electronic databases Pubmed, EMBASE, CENTRAL and Google Scholar, were searched for studies published between 1980 and 2018. Of 2049 screened studies, 125 articles were eligible for the meta-analyses. Complex I and IV were assessed in peripheral blood, muscle biopsy, or postmortem brain at the level of enzyme activity or subunits.

Separate meta-analyses of mood disorder studies, MDD and BD, revealed moderate effect sizes for similar abnormality patterns in the expression of complex I with SZ in frontal cortex, cerebellum and striatum, whereas evidence for complex IV alterations was low. By contrast, the neurodegenerative disorders, AD and PD, showed strong effect sizes for shared deficits in complex I and IV such as in peripheral blood, frontal cortex, cerebellum and substantia nigra. Beyond the diseased state, there was an age-related robust decline in both complexes I and IV. In summary, the strongest support for a role for complex I and/or IV deficits, is in the pathophysiology of PD and AD, and evidence is less robust for MDD, BD or SZ.

Introduction

Mitochondrial dysfunction is implicated in the pathophysiology of major psychiatric disorders, such as major depressive disorder (MDD) (Bansal and Kuhad, 2016), bipolar disorder (BD) (Kato, 2017) and schizophrenia (SZ) (Bergman and Ben-Shachar, 2016), as well as neurodegenerative disorders, such as Alzheimer disease (AD) (Onyango *et al*, 2017) and Parkinson disease (PD) (Onyango *et al*, 2017). Mitochondria are intracellular organelles that produce adenosine triphosphate (ATP), the main source of cellular energy. Impaired mitochondrial function results in decreased ATP production, impaired bioenergetics, apoptosis and oxidative stress (Hroudová and Fišar, 2011). Prior to the generation of ATP, mitochondria direct electrons extracted from nutrients into a transmembrane proton gradient and this process is mediated by the electron transport chain (ETC).

Research has identified two enzymes of the ETC located at the inner mitochondrial membrane as being particular impaired in these five disorders MDD, BD, SZ, AD and PD. The first enzyme, complex I (NADH dehydrogenase, NDU) consists of 45 subunits, seven of which are encoded by mitochondrial DNA (mtDNA) and the remaining subunits by nuclear DNA (nDNA). Complex I is one of the entry enzymes of cellular respiration or oxidative phosphorylation in the mitochondrion. It is also the largest multimeric enzyme complex of the ETC and is a major contributor to the generation of the proton gradient across the mitochondrial inner membrane, which drives ATP production. The second enzyme of interest, complex IV (cytochrome-c-oxidase, COX) consists of 13 subunits, three of which are encoded by mtDNA, the remainder by nDNA. Complex IV catalyzes the final step in the mitochondrial ETC and, due to its rate-limiting role in this oxidative process (Arnold, 2012), has been proposed as a key markers of mitochondrial function (Srinivasan and Avadhani, 2012). Numerous excellent reviews (Bansal and Kuhad, 2016; Bergman and Ben-Shachar, 2016; Kato, 2017; Onyango *et al*, 2017) have discussed the details of impairments in both

complex I and IV enzyme activities and subunit assembly within each of the above mentioned disorders. A meta-analysis summarizing the findings across these disorders could not be found in the literature. The remaining complexes II (succinate dehydrogenase), III (cytochrome c reductase) and V (ATP synthase) either have not been studied, or they have been studied to a much smaller degree in these five disorders, compared with complex I and IV, and thus there are too few data for a meta-analysis.

We chose these five disorders MDD, BD, SZ, AD and PD not only because of the potential common mitochondrial dysfunction, but also based on their clinical similarities. Though regarded as different disorders in major classification systems like DSM and ICD, there is also overlap in clinical symptoms. Depression is found in mood disorders, but is also frequent in schizophrenia and both AD and PD (Lanctôt *et al*, 2017; Zhuo *et al*, 2017). Psychotic symptoms are observed in MDD and BD as well as SZ ((DSM-IV-TR), 2000). Although Alzheimer's and Parkinson's diseases have distinct brain histopathology, both are age-related neurodegenerative conditions characterized by memory loss and depression and have some commonality in molecular pathogenesis, such as proteinopathy, neuroinflammation and oxidative stress (Aarsland *et al*, 2001). Cross-disorder commonalities are also found in schizophrenia sharing dopaminergic abnormalities with Parkinson's (Brisch *et al*, 2014) and cognitive impairment (dementia praecox) with Alzheimer's (Lyketsos CG and Peters ME, 2015).

Beyond disease states, normal aging plays an independent role in mitochondrial ETC function (Sun *et al*, 2016). To separate the influence of age from that of disease, we therefore additionally meta-analyzed complex I and IV functioning in healthy older versus younger individuals. The present meta-analyses aimed to provide a synthesis of the work done on complex I and IV that can guide future research and stimulate development of novel *in-vivo* technologies such as for example the assessment of the redox states of complex I

NAD+/NADH ratio (Blacker and Duchen, 2016; Zhu *et al*, 2015) or oxidized complex IV (Bale *et al*, 2016).

Materials and methods

Literature search and study identification

We conducted a structured literature search in PubMed, EMBASE, CENTRAL and Google Scholar, to identify studies published between January 1980 and January 2018 using the search strings 'NADH dehydrogenase' OR 'cytochrome-c-oxidase' OR 'complex I' OR 'complex IV' AND 'major depressive disorder' OR 'bipolar disorder' OR 'schizophrenia' OR 'Alzheimer' OR 'Parkinson' OR 'age/aging'. We manually reviewed reference lists in all retrieved articles for related publications.

Inclusion criteria were: studies investigated either complex I and/or complex IV, studies published in the English language, studies reporting original human data and studies that investigated patients in comparison with a control group. Exclusion criteria were: animal studies, cellular studies, genetic studies, studies with less than three subjects per group, case reports, letters to the editor and editorials and publications not reporting original data.

Data extraction

Aggregated data were extracted for each of the disorders MDD, BD, SZ, AD, PD and normal aging (AGING). Aggregated data contained quantitative data (i.e., number of patients and controls, mean age of patients and controls), qualitative information (i.e., methods such as enzyme activity or subunits at the level of mRNA or protein expression, and tissues assayed

such as peripheral blood, muscle or brain regions of interest, ROIs) and outcomes (effect sizes in terms of the standardized mean difference, SMD, and p-values). Enzyme activity was extracted as a corrected ratio to citrate synthase to normalize for mitochondrial content, if available. For studies on AGING, we chose a breakpoint of mean 60 years (Cabré *et al*, 2017) to derive group differences between older (> 60) and younger (< 60) individuals using t-test. In case of medication reported in the studies, both un-medicated and medicated cohorts were included. In case of BD, data were included from both BD I and BD II during depressive episodes, but not manic episodes.

The authors of some studies were contacted for permission to reuse original data (Altar *et al*, 2005; Karry *et al*, 2004; Konradi C *et al*, 2004; Manczak *et al*, 2004; Thomas *et al*, 2012; Washizuka *et al*, 2005, 2009); no answer was received in some cases and the data could therefore not or only partially included (Altar *et al*, 2005; Konradi C *et al*, 2004; Manczak *et al*, 2004; Thomas *et al*, 2012). Some data were read from figures (Andreazza *et al*, 2013; Andreazza AC *et al*, 2010; Cabré *et al*, 2017; Chagnon *et al*, 1995; Chandrasekaran *et al*, 1998; Devi *et al*, 2006; Distefano *et al*, 2017; Gatt *et al*, 2016; Gueugneau *et al*, 2015; Hsieh *et al*, 1994; Kim *et al*, 2016; Kish *et al*, 1992; Mehler-Wex *et al*, 2006; Munkholm *et al*, 2015; Mythri *et al*, 2011; Ojaimi *et al*, 1999; Parker *et al*, 2008; Safdar *et al*, 2010; Simonian and Hyman, 1993, 1995; Trounce *et al*, 1989).

Multivariate random-effect meta-analyses

Separate meta-analyses were first computed *for each disorder*. Moderator variables were generated representing the combination of two aspects: 1) method (enzyme activity or subunit); and 2) tissue (blood, muscle or ROI). A moderator was included in the meta-analysis only if it was reported by at least three studies. This threshold was chosen after extensive prior testing in order to avoid spurious results.

A summary meta-analysis was computed *across all disorders*. Here, the moderator variable consisted of the five disorders MDD, BD, SZ, AD, PD and AGING. This analysis included all data found to be eligible in the present work and thus also included rare outcomes that could not be included in the separate disease/aging meta-analyses.

For all meta-analyses, a multivariate random-effect model was applied based on the Metafor package (Viechtbauer, 2010) as implemented in R (R Development Core Team, 2008). The multivariate model accounts for heterogeneity and dependency in the underlying true effects of multiple moderators that can overlap within subjects and studies (random factors). To adjust for age effects, the age-difference between patients and controls was added as a continuous covariate. To adjust for sample size, the effects were weighted based on study size. To allow for heterogeneity differences between moderators, an unstructured variance-covariance matrix was applied (rma.mv function; observed effects = SMD + age-difference; variance-covariance matrix = COV; weight = study size; variance structure = UN; mods = moderators/disorder; random factors = subject/study; method = REML).

Forest plots were generated to illustrate the results of the multivariate models in terms of the weighted beta coefficients with 95% confidence intervals (CIs) and p-values. Heterogeneity was assessed using Cochran's Q-test and the inconsistency I^2 statistic that directly indicates to what extent each outcome contributes to the total variance. Publication bias was assessed using Egger's regression analysis.

Results

Data extraction

Of 2049 screened studies, 125 studies were eligible for the meta-analyses, some of them for more than one disorder (MDD N = 7, BD N = 19, SZ N = 21, AD N = 43, PD N = 35, AGING N = 18) (**Table 1**). The overall number of studies reporting on complex I (total N = 101, MDD N = 6, BD N = 19, SZ N = 15, AD N = 19, PD N = 32, AGING N = 11) and complex IV (total N = 104, MDD N = 4, BD N = 10, SZ N = 10, AD N = 39, PD N = 28, AGING N = 15) were similar but varied between disorders. Both complex I and IV were analysed in either peripheral blood elements, such as platelets, lymphocytes or other blood cells (MDD N = 1, BD N = 10, SZ N = 8, AD N = 9, PD N = 14, AGING N = 2), in muscle biopsies (MDD N = 2, BD N = 0, SZ N = 0, AD N = 0, PD N = 9, AGING N = 14), or in postmortem brain samples (MDD N = 4, BD N = 8, SZ N = 13, AD N = 34, PD N = 14, AGING N = 2). Both complex I and IV were analysed at the level of enzymatic activity (either in blood, muscle, or brain, MDD N = 4, BD N = 5, SZ N = 11, AD N = 32, PD N = 32, AGING N = 14), or of their subunits by mRNA level (only brain, MDD N = 3, BD N = 7, SZ N = 7, AD N = 7, PD N = 1, AGING N = 2) or protein level (only brain, MDD N = 3, BD N = 12, SZ N = 7, AD N = 6, PD N = 3, AGING N = 5). In the following, enzyme activity is denoted with NDU/COX respectively, whereas subunits as assessed by either mRNA or protein expression are referred to with their full names.

Note that we combined data from levels of mRNA/protein expression for all subunits. The correlation between mRNA and protein expression is generally thought to be around 40% (Abreu et al, 2009; Vogel and Marcotte, 2012), which is typically attributed to other levels of regulation between transcript and protein product **(Maier *et al*, 2009)**. We separated the

findings in a pre-analysis but found no significant differences between mRNA and protein expression and therefore presented the results together.

Assay of enzyme activity was more common in studies of neurodegenerative disorders, AD (88%) and PD (66%), whereas the assessment of mRNA/protein expression was more common in studies of mood disorders, MDD (60%), BD (79%) and SZ (56%). None of the five disorders, however, showed differences in enzyme activity or mRNA/protein expression for complex I or IV ($p > 0.05$). Moreover, there were no differences between peripheral blood and brain in the enzyme activity/mRNA/protein levels of complex I and IV ($p > 0.05$).

All studies involved subjects over 18 years old, except two studies examined early-onset SZ patients below age 18 years (Mehler-Wex *et al*, 2006; Taurines *et al*, 2010). The mean age-difference between cases and controls differed between disorders (main effect $F = 35.21$, $p < 0.0001$). Psychiatric studies, MDD (mean age-difference ± STD = -0.7 ± 3.9), BD (mean age-difference ± STD = 0.8 ± 4.9) and SZ (mean age-difference ± STD = -1.0 ± 3.7) included closer age-matched cases and controls compared with AD (mean age-difference ± STD = 5.0 ± 7.5) or PD (mean age-difference ± STD = 5.3 ± 5.9) as indicated by significant post-hoc comparisons ($p < 0.0001$). Some studies did not provide mean ages for cases and/or controls (Cooper *et al*, 1993; DiDonato *et al*, 1993; Hirai *et al*, 2001; Reichmann *et al*, 1993; Wiedemann *et al*, 1999), for which we therefore assumed zero age-difference.

Multivariate random-effect meta-analyses

Meta-analyses were performed for each of the disorders MDD, BD, SZ, AD, PD and AGING. Based on the precondition that a moderator was reported at least three times across studies, the number of studies finally included in the meta-analyses (and the percentage of the eligible studies) differed between disorders MDD (complex I N = 4 (67%), complex IV N = 2 (50%)),

BD (complex I N = 16 (84%), complex IV N = 3 (30%)), SZ (complex I N = 14 (93%), complex IV N = 6 (60%)), AD (complex I N = 12 (63%), complex IV N = 33 (85%)), PD (complex I N = 29 (91%), complex IV N = 24 (86%) and AGING (complex I N = 7 (64%), complex IV N = 14 (93%)).

Mood disorders

In MDD (**Figure 1a**), complex I subunits $NDUFS1_{cerebellum}$ ($p = 0.0075$), $NDUFV1_{cerebellum}$ ($p = 0.00014$) and $NDUFV2_{cerebellum}$ ($p = 0.00051$) were lower in cerebellum and subunit $NDUFV1_{frontal}$ ($p = 0.0047$) was lower in frontal cortex compared with controls. No differences were found for complex IV (note that only in this case, we set the moderator threshold to at least two).

In BD (**Figure 1b**), complex I subunit $NDUFS1_{cerebellum}$ ($p < 0.0001$) was lower in cerebellum, subunits $NDUFS1_{frontal}$ ($p = 0.033$) and $NDUFS7_{frontal}$ ($p < 0.0001$) were lower in frontal cortex and subunit $NDUFS1_{striatum}$ ($p = 0.0023$) was lower in striatum compared with controls. No differences were found for complex IV.

In SZ (**Figure 1c**), complex I subunit $NDUFV2_{blood}$ ($p = 0.019$) was lower in blood, whereas subunit $NDUFS1_{blood}$ ($p = 0.00086$) was higher in blood compared with controls. Further, subunits $NDUFS1_{striatum}$ ($p = 0.00072$), $NDUFV1_{striatum}$ ($p < 0.0001$) and $NDUFV2_{striatum}$ ($p < 0.0001$) were lower in striatum, subunit $NDUFV1_{frontal}$ ($p = 0.011$) was lower in frontal cortex, whereas subunit $NDUFV2_{parietal}$ ($p = 0.019$) was higher in parietal cortex compared with controls. Complex IV enzyme activity was lower in frontal cortex ($COX_{frontal}$ $p = 0.016$), but higher in basal ganglia ($COX_{NA/GP/P}$ $p< 0.0001$, nucleus accumbens, globus pallidus and putamen) compared with controls.

We also assessed the overlap in findings between MDD, BD and SZ using meta-regressions. Results confirmed lower NDUFS1/NDUFV1/NDUFV2 levels in the cerebellum in MDD ($p =$

0.005/p = 0.001/p = 0.006) and in some subunits also BD (p = 0.088/p = 0.001/p = 0.258) compared to SZ, respectively. By contrast, lower NDUFS1/NDUFV1/NDUFV2 levels in striatum were observed in SZ compared to MDD (p = 0.001/p < 0.0001/p < 0.0001) and in some subunits also BD (p = 0.250/p < 0.0001/p < 0.0001), respectively. Further, both BD (p = 0.024) and SZ (p = 0.008) revealed higher levels of NDUFV2 in the parietal cortex compared to MDD. Last, in BD, subunit $NDUFS1_{blood}$ levels (p = 0.002) in blood and subunit $NDUFS7_{frontal}$ (p = 0.009) in frontal cortex were lower compared to SZ.

Neurodegenerative disorders

In AD (**Figure 2a**), complex I enzyme activity in the temporal cortex ($NDU_{temporal/entorhinal}$ p = 0.0023) and subunits $NDUFA1/4/7\text{-}9_{blood}$ (p < 0.0001), $NDUFB2/3/6_{blood}$ (p < 0.0001) and $NDUFS3/4/5_{blood}$ (p < 0.0001) were lower in blood compared with controls. It should be noted that these subunits were reported by Lunnon et al. (Lunnon *et al*, 2012), which was the largest study eligible for the present work with a total of 209 subjects (patients N = 104, controls N = 105). Initially only a small subset of that study could be included in the meta-analysis because of the high moderator threshold; in order to include more of the results from that study, we summarized results across subunits to build sufficient moderators.

Complex IV enzyme activity was lower in frontal cortex ($COX_{frontal}$ p = 0.044), motor cortex (COX_{motor} p = 0.0003), occipital cortex ($COX_{occiptal}$ p = 0.032), parietal cortex ($COX_{parietal}$ p = 0.00069), temporal/entorhinal cortex ($COX_{temporal/entorhinal}$ p = 0.00012) and hippocampus ($COX_{hippocampus}$ p < 0.0001) compared to controls. Subunit $COX2_{hippocampus}$ in hippocampus (p < 0.0001) and subunit $COX7_{blood}$ in peripheral blood (p = 0.011) were lower.

In PD (**Figure 2b**), complex I enzyme activity in peripheral muscle (NDU_{muscle} p = 0.000084) as well as in substantia nigra ($NDU_{substantia\ nigra}$ p = 0.006) was lower compared to controls. Complex IV enzyme activity in frontal cortex ($COX_{frontal}$ p = 0.036) was also lower.

The overlap between AD and PD was assessed using meta-regressions. Results showed comparable patterns of enzyme activity in blood (COX_{blood} $p = 0.981$) and brain such as in frontal cortex ($NDU_{frontal}$ $p = 0.171$, $COX_{frontal}$ $p = 0.711$), cerebellum ($COX_{cerebellum}$ $p = 0.582$) and substantia nigra ($COX_{substantia\ nigra}$ $p = 0.671$), indicating no significant differences between AD and PD.

Aging

To assess complex I and IV functioning in normal aging, we performed a separate meta-analysis in healthy subjects using a breakpoint of 60 years (Cabré *et al*, 2017) (**Figure 2c**). Older (≥ 60 years) subjects in comparison with younger (< 60 years) subjects had lower complex I enzyme activity in frontal cortex ($NDU_{frontal}$ $p < 0.0001$) and muscle (NDU_{muscle} $p < 0.0001$, $NDUFB8_{muscle}$ $p = 0.00015$). Similarly, complex IV enzyme activity was lower in frontal cortex ($COX_{frontal}$ $p = 0.00072$) and muscle (COX_{muscle} $p = 0.00027$, $COX2_{muscle}$ $p < 0.0001$) in older compared to younger subjects.

Summary comparison of all cases and controls

A summary meta-analysis was performed to categorize the disorders according to the severity of overall mitochondrial impairments (**Figure 3**). Robust deficits were observed for complex I in PD ($p = 0.0016$) and AGING ($p = 0.009$) and for complex IV in AD ($p = 0.004$) and AGING ($p < 0.0001$). MDD ($p < 0.0001$) also showed an effect on complex I; however, it was based on small samples sizes from few studies and can therefore not be considered a robust result. The main effect across both complex I and IV was significant in PD ($p = 0.00058$), AD ($p = 0.049$) and AGING ($p < 0.0001$) indicating that these three conditions were also affected if both complex I and IV are considered.

Heterogeneity and publication bias

Overall, there was a high degree of heterogeneity (**Table 2**). The I^2 for the five disorders MDD, BD, SZ, AD and PD ranged between 80-100%. Noticeable, there was low heterogeneity in AGING in both complex I ($Q = 27.934$, $p = 0.218$, $I^2 = 18\%$) and IV ($Q = 11.684$, $p = 1$, $I^2 = 0\%$). Putative low heterogeneity was observed in MDD for complex IV ($Q = 0.030$, $p = 1$, $I^2 = 0\%$), most likely explained by the fact that the data came from few studies ($N = 4$).

Publication bias as assessed using Egger's regression test (**Table 2**) provided non-significant results for most of the data indicating no publication bias. Considerable publication bias was only found in PD for complex I ($p = 0.043$) and in AGING for complex IV ($p = 0.014$).

Discussion

Our findings provide a picture of the current findings on complex I and IV in mood and neurodegenerative disorders (**Figure 4**). We found that mood disorders, MDD and BD, share commonalities with SZ in having low expression of complex I subunits. Neurodegenerative disorders, AD and PD, share similarities in complex I and IV enzyme activity abnormalities. Due to heterogeneity in study findings, strong evidence for complex I and/or IV deficits is present for AD and PD, whereas the overall proof for the involvement of these complexes in MDD, BD and SZ is less robust and requires further research. Normal aging is a substantial independent factor contributing to both complex I and IV decline and should be considered when interpreting study heterogeneity.

Mood disorders

Mood disorders show shared patterns of complex I subunits NDUFS1, NDUFV1 and NDUFV2 between MDD and BD on the one hand, and between BD and SZ on the other hand (**Figure 1**) (Andreazza *et al*, 2013; Andreazza AC *et al*, 2010; Ben-Shachar and Karry, 2008; Iwamoto *et al*, 2005; Karry *et al*, 2004; Kim *et al*, 2016; Sun *et al*, 2006). While, MDD and to some degree BD, have lower levels of NDUFS1, NDUFV1, NDUFV2 in cerebellum compared with SZ, the latter had lower NDUFS1, NDUFV1, NDUFV2 levels in striatum compared with MDD and to some degree BD; this indicates a shared mechanism between MDD and BD that is distinct from SZ. By contrast, BD and SZ had elevated levels of NDUFV2 in parietal cortex compared with MDD, which may indicate a shared mechanism between BD and SZ. These brain regions, i.e., the frontal cortex (Brakowski *et al*, 2017; Hibar *et al*, 2017), cerebellum (Jiang *et al*, 2017; Shinn *et al*, 2017) and striatum (Pacifico and Davis, 2016), have been previously suggested to contribute to the pathophysiology of mood disorders and schizophrenia spectrum (Dietsche *et al*, 2017). Distinct from the mood

disorders, SZ has higher complex IV levels in basal ganglia (Prince *et al*, 1999, 2000) perhaps related to previous neuropathological findings in putamen, nucleus accumbens and globus pallidus (Mamah *et al*, 2007; Womer *et al*, 2014).

Notably, while most of the eligible studies pointed to dysregulation of complex I and/or IV, the reported direction of change has not always been consistent. While some of the heterogeneity may be due to potential differences in the clinical picture like presence of psychosis in MDD or BD and presence of depression in SZ, several other explanations may underlie these discrepancies. First, there may be state-related differences in the expression of complex I and IV. For example BD patients showed up-regulation of complex I subunits during manic compared to depressive episodes (Akarsu *et al*, 2015) maybe related to elevated brain metabolism in frontal and temporal cortex (Shao *et al*, 2008). Similarly in SZ, state-dependence has been suggested with increased complex I activity in active psychotic patients but decreased activity in patients with residual schizophrenia (Ben-Shachar *et al*, 2007; Dror *et al*, 2002; Rosenfeld *et al*, 2011). Unfortunately, postmortem studies were unable to provide information on whether patients were depressed, manic or euthymic at time of death. Second, there may be brain region-specific heterogeneity, possibly indicating that ETC energy production varies from region to region, as previously exemplarily shown (Ben-Shachar and Karry, 2008). Third, there may be tissue-specific differences between blood samples from living patients and brain samples obtained postmortem. For example, it has been hypothesized that ETC genes are up-regulated in blood, but down-regulated in some or all brain regions in BD (Beech et al, 2010) and SZ (Ben-Shachar and Karry, 2007), although this was not confirmed statistically by the present meta-analysis. Fourth, the majority of patients were receiving psychotropic medication, such as antidepressants, mood stabilizers and antipsychotics. All of these pharmacological agents have been reported to potentially interfere or even inhibit the mitochondrial ETC (Manji et al, 2012). Finally, differences in brain pH at

the time of death may explain difference in gene expression (Vawter *et al*, 2006). Larger sample studies of medication-free patients are needed to clarify more precisely the relationships between diagnosis, mood state, treatment status and brain pH in mood disorders and schizophrenia pathophysiology. There is also evidence of shared global gene expression patterns between mood disorders and schizophrenia that go beyond purely mitochondrial function that could be investigated in relation (Gandal *et al*, 2018).

Neurodegenerative disorders

Neurodegenerative disorders AD and PD show similarities in the impairment of complex I and IV enzyme activities in the blood, frontal cortex, cerebellum and substantia nigra (**Figure 2**). These brain regions are potentially involved in the cognitive decline and neuronal loss in AD (Boublay *et al*, 2016; Perluigi *et al*, 2016) as well as in the motor and non-motor related degeneration of neurotransmitter systems in PD (Atkinson-Clement *et al*, 2017; Gao and Wu, 2016).

In AD, there are a well-documented deficit in both complex I and IV (Coskun et al, 2012; Giachin et al, 2016; Onyango et al, 2017). These deficits are thought to be due to the neuronal toxicity induced by amyloid β peptide (Aβ), an important component of AD pathogenesis, in that Aβ accumulates in mitochondria, directly inhibits mitochondrial enzymes, perpetuates oxidative stress, and leads to a hypometabolic state, which causes mitochondrial dysfunction (Cenini et al, 2016; Picone et al, 2014; Pinho et al, 2014; Readnower et al, 2011). The meta-analysis supported these findings in terms of down-regulated complex I and IV in the blood (Cardoso *et al*, 2004; Feldhaus *et al*, 2011; Fišar *et al*, 2016; Lunnon *et al*, 2012; Mancuso *et al*, 2003; Parker *et al*, 1990, 1994a; Sheehan *et al*, 1997; Valla *et al*, 2006), frontal cortex (Cavelier *et al*, 1995; Devi *et al*, 2006; Hirai *et al*, 2001; Kish *et al*, 1992; Long *et al*, 2012; Maurer *et al*, 2000; Parker *et al*, 1994b; Pérez-Gracia *et al*, 2008; Wong-Riley *et al*, 1997),

motor cortex (Bosetti *et al*, 2002; Valla *et al*, 2001; Wong-Riley *et al*, 1997), occipital cortex (Kish *et al*, 1992, 1999; Mutisya *et al*, 1994), parietal cortex (Chagnon *et al*, 1995; Kish *et al*, 1992, 1999; Mutisya *et al*, 1994; Reichmann *et al*, 1993; Wong-Riley *et al*, 1997), temporal/entorhinal cortex (Alikhani *et al*, 2011; Chandrasekaran *et al*, 1998; Cooper *et al*, 1993; Gu *et al*, 1998; Kish *et al*, 1992, 1999; Maurer *et al*, 2000; Mutisya *et al*, 1994; Reichmann *et al*, 1993; Wong-Riley *et al*, 1997) and hippocampus (Aksenov *et al*, 1999; Bosetti *et al*, 2002; Chagnon *et al*, 1995; Chandrasekaran *et al*, 1994; Cottrell *et al*, 2001; Kish *et al*, 1992; Maurer *et al*, 2000; Reichmann *et al*, 1993; Simonian and Hyman, 1993, 1995; Verwer *et al*, 2000; Wong-Riley *et al*, 1997). The strength of the effect sizes are in line with findings of neuronal loss in entorhinal cortex, hippocampus and association neocortex (Perluigi *et al*, 2016). Due to limited data, the meta-analysis was not able to distinguish between Brack stages in AD. A large study in AD (N = 148) reported less expression of complex I and IV subunits in entorhinal and frontal cortex in disease stages V-VI but not in stages I -II (Armand-Ugon *et al*, 2017). A smaller study (N = 18) compared complex I and IV enzyme activity in frontal cortex in stages III-VI to stages I-II but found no stage-dependence (Manczak *et al*, 2004). There were also no differences between early- versus late-onset AD (age < 60 versus age > 60) (Cardoso *et al*, 2004).

In PD, the meta-analysis points to down-regulation of both complex I and IV enzyme activity in the blood, muscle and brain. For example, inhibition of complex I has been reported in platelets (Benecke *et al*, 1993; Blake *et al*, 1997; Bravi *et al*, 1992; Gu *et al*, 1998; Krige *et al*, 1992; Parker *et al*, 1989; Varghese *et al*, 2009; Yoshino *et al*, 1992) and skeletal muscles (Bindoff *et al*, 1991; Blin *et al*, 1994; Cardellach *et al*, 1993; Nakagawa-Hattori *et al*, 1992; Shoffner *et al*, 1991), although there was dissenting studies in platelets (Bronstein *et al*, 2015; Martín *et al*, 1996) or muscle (Anderson *et al*, 1993; DiDonato *et al*, 1993; Mann *et al*, 1992). Similarly, complex IV has been found to be decreased in blood (Benecke *et al*, 1993; Bravi *et*

al, 1992; Haas *et al*, 1995; Krige *et al*, 1992; Parker *et al*, 1989; Shinde and Pasupathy, 2006) and muscle (Anderson *et al*, 1993; Bindoff *et al*, 1991; Cardellach *et al*, 1993; Shoffner *et al*, 1991), while others could not confirm this for either platelets (Blake *et al*, 1997; Hanagasi *et al*, 2005) or muscle (Blin *et al*, 1994; DiDonato *et al*, 1993; Mann *et al*, 1992; Nakagawa-Hattori *et al*, 1992; Wiedemann *et al*, 1999). Within the brain, some studies reported lower complex I enzyme activity in substantia nigra (Gu *et al*, 1998; Mann *et al*, 1992; Mizuno *et al*, 1990; Schägger, 1995; Schapira *et al*, 1990b) as well as low activity and impaired assembly of complex I in frontal cortex (Barroso *et al*, 1993; Gatt *et al*, 2016; Keeney *et al*, 2006; Mizuno *et al*, 1990; Mythri *et al*, 2011; Parker *et al*, 2008), the latter not being confirmed in the meta-analysis. Similarly, complex IV in the brain is reported to be low in frontal cortex (Barroso *et al*, 1993; Chagnon *et al*, 1995; Keeney *et al*, 2006; Mizuno *et al*, 1990; Parker *et al*, 2008) and substantia nigra (Chagnon *et al*, 1995; Gu *et al*, 1998; Mann *et al*, 1992; Schägger, 1995; Schapira *et al*, 1990a), the latter finding not confirmed here. Note that although all data eligible for the meta-analysis were obtained from patients suffering from the more common sporadic form of PD, derangements in mitochondrial metabolism and oxidative stress have also been strongly linked to the less common familial form of PD (Ryan *et al*, 2015).

Likewise for mood disorders, medication may affect mitochondrial functioning in neurodegeneration. Cholinesterase (ChE) inhibitors and amyloid-beta binding alcohol dehydrogenase (ABAD) modulators are used to treat the key symptoms in AD in order to improve activities of daily living, behavior and cognition (Grossberg, 2003). Most of these drugs can negatively affect both complex I and IV (Hroudová et al, 2017). There are however newly developed ChEs and ABADs as well as other more recent drug developments that target multiple AD pathophysiological pathways that are thought to have a better outcome on mitochondrial function (Korábečný *et al*, 2018). By contrast, in PD, levodopa, cardidopa, and

selegiline, which are used to treat PD motor symptoms, have not been shown not affect complex I and IV in PD (Dixit et al, 2013; Shults et al, 1995). Similarly, melatonin that is used as sleep/wake regulator in PD, acts as an effective antioxidant and mitochondrial function protector (Srinivasan et al, 2011). These observations support the hypothesis that impaired complex I and IV activity in PD patients is a characteristic of the disease and not due to medications.

Aging

Normal aging has been associated with a decline in mitochondrial quality (Sun *et al*, 2016) and activity of both complex I and IV (Arnold, 2012; Navarro and Boveris, 2007). The meta-analysis supported these findings in terms of decreased levels of enzyme activity in the muscle (Boffoli *et al*, 1996; Distefano *et al*, 2017; Emelyanova *et al*, 2017; Gueugneau *et al*, 2015; Hsieh *et al*, 1994; Lanza *et al*, 2008; Ogborn *et al*, 2015; Pestronk *et al*, 2017; Rooyackers *et al*, 1996; Safdar *et al*, 2010; Zucchini *et al*, 1995) and frontal cortex (Boffoli *et al*, 1994, 1996; Cabré *et al*, 2017; Ojaimi *et al*, 1999) (**Figure 2c**). Across all meta-analyses, the effect of aging was the most robust both in terms of the strength of the summary effect sizes (**Figure 3**) as well as the low degree of heterogeneity (**Table 2**).

The decline in both complex I and IV in normal aging (Arnold, 2012; Navarro and Boveris, 2007) as indicated by this meta-analysis can represent a functionally serious impairment of mitochondrial function with respect to basal ATP production (Boveris *et al*, 1999). Therefore, aged neurons with lower mitochondrial mass and enzyme activities as well as more dysfunctional mitochondria may be unable to respond adequately to any increased ATP demand (Navarro and Boveris, 2004).

The term normal aging should be considered carefully. Normal aging is thought to be a function of both chronological age as well as biological age (Safdar et al, 2010). Although the

underlying mechanism is still controversial, age-dependent mitochondrial decline may contribute to loss of physical capacity and mental exertion (Christian and Shadel, 2014; Payne and Chinnery, 2015). The 'free radical' theories of aging (Harman, 1992; Miquel *et al*, 1980) state that reactive oxygen species (ROS) produced aberrantly during mitochondrial electron transport damage mitochondrial components, including mtDNA. Since, mtDNA encodes essential complex I and IV proteins (Bonawitz *et al*, 2006), its damage and mutagenesis would disrupt ETC complex assembly and, in turn, lead to more ROS production, cellular oxidative stress and tissue dysfunction that promote aging (Mandavilli *et al*, 2002). This theory, however, has been thought to be too simplistic and there is debate about other age-dependent cellular changes that may be as important in precipitating the decline in mitochondrial ETC (Christian and Shadel, 2014).

Summary comparison of all cases and controls

Summarizing the overall severity of mitochondrial impairment in the five disorders (**Figure 3**) indicates that major psychiatric disorders MDD, BD and SZ show less robust effects. The small effect sizes in those pathologies were most likely due to the small number of studies with small sample sizes, large region-specific heterogeneity and variation in medication and treatment, which made in harder to detect underlying mitochondrial disease. By contrast, strong evidence for a complex I deficit is found in PD, whereas a complex IV deficit is present in AD; with the simultaneous decline in complex I and IV being significant in both AD and PD. These results indicate an interaction of complex I with IV involved in the assembly and stability of complex I (Diaz *et al*, 2006; Li *et al*, 2007; Schäfer *et al*, 2007).

The interpretation of the strengths of the effect sizes between the five disorder compared with normal aging, as shown in **Figure 3**, should however be cautious. Aging is a major risk factor for developing both AD (Swerdlow, 2011) and idiopathic PD (Reeve *et al*, 2014).

Consequently, the effects of normal aging and that of the diseases cannot be clearly separated because of their inter-dependence. Of note, patients in all studies included were age-matched, thus in principle presenting age-adjusted effects. We therefore argue that the lesser effects in mood disorders is not related to the younger age of these patients, and the larger effects in AD is also not related to older age.

Further research is required to enlarge sample sizes and strengthen the evidence base. Our results may stimulate the application of novel in-vivo technologies such as assessing complex I NAD+/NADH redox state via auto-fluorescence (Blacker and Duchen, 2016) or magnetic resonance spectroscopy (Zhu *et al*, 2015) and complex IV redox states via functional near-infrared spectroscopy (Bale *et al*, 2016).

Supplementary materials

Datasets 1-6: Datasets collected for the disorders MDD, BD, SZ, AD, PD and AGING.

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Figure legends

Figure 1. Forest plots MDD, BD and SZ. Multivariate random-effect estimates of the SMD (95% CI, p-values) of complex I (NDU) and IV (COX) enzyme activity and subunits are shown both in numerical and graphical form. Values lower than 0 indicate that patients had lower levels than controls (CO), and vice versa for values greater than 0; the dashed vertical line at SMD = 0 indicates no effect. The size of the filled circles for each estimated SMD is proportional to the weight of the studies. P = putamen, NA = nucleus accumbens, GP = globus pallidus.

Figure 2. Forest plots AD, PD and AGING. Multivariate random-effect estimates of the SMD (95% CI, p-values) of complex I (NDU) and IV (COX) enzyme activity and subunits are shown both in numerical and graphical form. Values lower than 0 indicate that patients (or older (O) individuals) had lower levels than controls (CO) (or younger (Y) individuals), and vice versa for values greater than 0; the dashed vertical line at SMD = 0 indicates no effect. The size of the filled circles for each estimated SMD is proportional to the weight of the studies.

Figure 3. Forest plot Summary. Multivariate random-effect estimates of the SMD (95% CI, p-values) of complex I and IV are shown both in numerical and graphical form. SMD are ordered according to their strengths. Values lower than 0 indicate that patients (P) had lower levels than controls (CO), and vice versa for values greater than 0; the dashed vertical line at SMD = 0 indicates no effect. The size of the filled circles for each estimated SMD is proportional to the weight of the studies.

Figure 4. Schematic overview of our findings. Highlighted are the main findings of the meta-analyses for the five disorders MDD, BD, SZ, AD, PD and normal aging. Region-specific heterogeneity means that complex levels vary from brain region to brain region (i.e.,

variation from ROI to ROI); tissue-specific heterogeneity indicates that complex levels vary between tissues (i.e., peripheral blood versus brain).

Tables

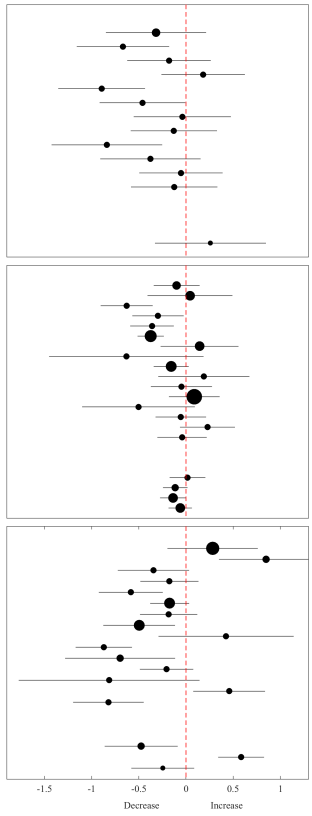
Table 1. Eligible studies. 125 studies were eligible for the meta-analyses, part of which was included in the meta-analyses for complex I and IV (marked in gray). Some studies reported more than one disorder. The detailed data extracted from these studies are provided in the supplementary materials (**Tables S1-6**).

MDD (N = 7)	BD (N = 19)	SZ (N = 21)	AD (N = 43)	PD (N = 35)	AGING (N = 18)
Andreazza 2010 (Andreazza AC *et al*, 2010)	Akarsu 2015 (Akarsu *et al*, 2015)	Altar 2005 (Altar *et al*, 2005)	Aksenov 1999 (Aksenov *et al*, 1999)	Anderson 1993 (Anderson *et al*, 1993)	Boffoli 1994 (Boffoli *et al*, 1994)
Ben-Shachar 1999 (Ben-Shachar *et al*, 1999)	Altar 2005 (Altar *et al*, 2005)	Andreazza 2010 (Andreazza AC *et al*, 2010)	Alikhani 2012 (Alikhani *et al*, 2011)	Barroso 1993 (Barroso *et al*, 1993)	Boffoli 1996 (Boffoli *et al*, 1996)
Ben-Shachar 2008 (Ben-Shachar and Karry, 2008)	Andreazza 2010 (Andreazza AC *et al*, 2010)	Andreazza 2013 (Andreazza *et al*, 2013)	Armand-Ugon 2017 (Armand-Ugon *et al*, 2017)	Benecke 1993 (Benecke *et al*, 1993)	Cabré 2017 (Cabré *et al*, 2017)
Gardner 2003 (Gardner *et al*, 2003)	Andreazza 2013 (Andreazza *et al*, 2013)	Ben-Shachar 1999 (Ben-Shachar *et al*, 1999)	Bosetti 2002 (Bosetti *et al*, 2002)	Bindoff 1991 (Bindoff *et al*, 1991)	Distefano 2017 (Distefano *et al*, 2017)
Gardner 2008 (Gardner *et al*, 2008)	Beech 2010 (Beech *et al*, 2010)	Ben-Shachar 2007 (Ben-Shachar *et al*, 2007)	Cardoso 2004 (Cardoso *et al*, 2004)	Blake 1997 (Blake *et al*, 1997)	Emelyanova 2017 (Emelyanova *et al*, 2017)
Karry 2004 (Karry *et al*, 2004)	Ben-Shachar 1999 (Ben-Shachar *et al*, 1999)	Ben-Shachar 2008 (Ben-Shachar and Karry, 2008)	Casademont 2005 (Casademont *et al*, 2005)	Blin 1994 (Blin *et al*, 1994)	Gueugneau 2014 (Gueugneau *et al*, 2015)
Sanchez-Bahillo 2008 (Sanchez-Bahillo *et al*, 2008)	Ben-Shachar 2008 (Ben-Shachar and Karry, 2008)	Cavelier 1995 (Cavelier *et al*, 1995)	Cavelier 1995 (Cavelier *et al*, 1995)	Bravi 1992 (Bravi *et al*, 1992)	Hsieh 1994 (Hsieh *et al*, 1994)
	de Sousa 2015 (de Sousa *et al*, 2015)	Dror 2002 (Dror *et al*, 2002)	Chagnon 1995 (Chagnon *et al*, 1995)	Bronstein 2015 (Bronstein *et al*, 2015)	Lanza 2008 (Lanza *et al*, 2008)
	Gubert 2013 (Gubert *et al*, 2013)	Gubert 2013 (Gubert *et al*, 2013)	Chandrasekaran 1994 (Chandrasekaran *et al*, 1994)	Cardellach 1993 (Cardellach *et al*, 1993)	Merlo Pich 2004 (Merlo Pich *et al*, 2004)
	Iwamoto 2005 (Iwamoto *et al*, 2005)	Iwamoto 2005 (Iwamoto *et al*, 2005)	Chandrasekaran 1998 (Chandrasekaran *et al*, 1998)	Chagnon 1995 (Chagnon *et al*, 1995)	Merlo Pich 1996 (Merlo Pich *et al*, 1996)
	Karry 2004 (Karry *et al*, 2004)	Karry 2004 (Karry *et al*, 2004)	Cooper 1993 (Cooper *et al*, 1993)	Cooper 1995 (Cooper *et al*, 1995)	Ogborn 2015 (Ogborn *et al*, 2015)
	Kim 2016 (Kim *et al*, 2016)	Kim 2016 (Kim *et al*, 2016)	Cottrell 2001 (Cottrell *et al*, 2001)	DiDonato 1993 (DiDonato *et al*, 1993)	Ojaimi 1999 (Ojaimi *et al*, 1999)
	Konradi 2004 (Konradi C *et al*, 2004)	Maurer 2001 (Maurer *et al*, 2001)	Devi 2006 (Devi *et al*, 2006)	Duke 2007 (Duke *et al*, 2007)	Pestronk 2016 (Pestronk *et al*, 2017)
	Munkholm 2015 (Munkholm *et al*, 2015)	Mehler-Wex 2006 (Mehler-Wex *et al*, 2006)	Feldhaus 2011 (Feldhaus *et al*, 2011)	Gatt 2016 (Gatt *et al*, 2016)	Rasmussen 2003 (Rasmussen *et al*, 2003)
	Naydenov 2007 (Naydenov AV *et al*, 2007)	Prince 1999 (Prince *et al*, 1999)	Fišar 2016 (Fišar *et al*, 2016)	Gu 1998 (Gu *et al*, 1998)	Rooyackers 1996 (Rooyackers *et al*, 1996)
	Rosenfeld 2011 (Rosenfeld *et al*, 2011)	Prince 2000 (Prince *et al*, 2000)	Fukuyama 1996 (Fukuyama *et al*, 1996)	Haas 1995 (Haas *et al*, 1995)	Safdar 2010 (Safdar *et al*, 2010)
	Sun 2006 (Sun *et al*, 2006)	Rice 2014 (Rice *et al*, 2014)	Gu 1998 (Gu *et al*, 1998)	Hanagasi 2004 (Hanagasi *et al*, 2005)	Trounce 1989 (Trounce *et al*, 1989)
	Washizuka 2005 (Washizuka *et al*, 2005)	Rosenfeld 2011 (Rosenfeld *et al*, 2011)	Hirai 2001 (Hirai *et al*, 2001)	Keeney 2006 (Keeney *et al*, 2006)	Zucchini 1995 (Zucchini *et al*, 1995)
	Washizuka 2009 (Washizuka *et al*, 2009)	Taurines 2010 (Taurines *et al*, 2010)	Kim 2001 (Kim *et al*, 2001)	Krige 1992 (Krige *et al*, 1992)	
		Washizuka 2009 (Washizuka *et al*, 2009)	Kish 1992 (Kish *et al*, 1992)	Mann 1992 (Mann *et al*, 1992)	
		Whatley 1998 (Whatley *et al*, 1996)	Kish 1999 (Kish *et al*, 1999)	Martín 1996 (Martín *et al*, 1996)	
			Liang 2008 (Liang *et al*, 2008)	Mizuno 1990 (Mizuno *et al*, 1990)	
			Long 2012 (Long *et al*, 2012)	Mythri 2011 (Mythri *et al*, 2011)	
			Lunnon 2012 (Lunnon *et al*, 2012)	Nakagawa-Hattori 1992 (Nakagawa-Hattori *et al*, 1992)	
			Mancuso 2003 (Mancuso *et al*, 2003)	Parker 1989 (Parker *et al*, 1989)	

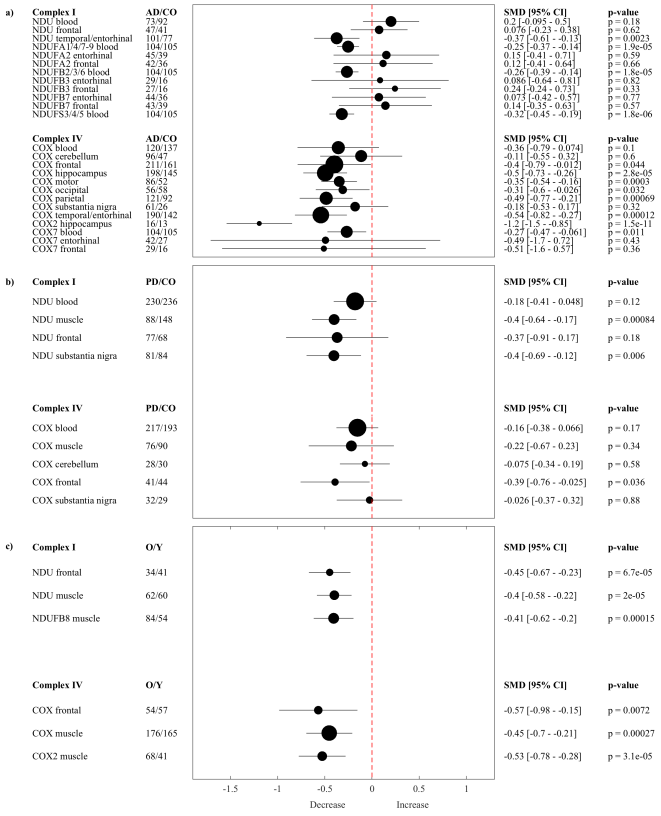
			Manczak 2004 (Manczak *et al*, 2004)	Parker 2008 (Parker *et al*, 2008)	
			Maurer 2000 (Maurer *et al*, 2000)	Schaegger 1995 (Schägger, 1995)	
			Mutisya 1994 (Mutisya *et al*, 1994)	Schapira 1990a (Schapira *et al*, 1990a)	
			Parker 1990 (Parker *et al*, 1990)	Schapira 1990b (Schapira *et al*, 1990b)	
			Parker 1994a (Parker *et al*, 1994b)	Shinde 2006 (Shinde and Pasupathy, 2006)	
			Parker 1994b (Parker *et al*, 1994a)	Shoffner 1991 (Shoffner *et al*, 1991)	
			Pérez-Gracia 2008 (Pérez-Gracia *et al*, 2008)	Thomas 2012 (Thomas *et al*, 2012)	
			Reichmann 1993 (Reichmann *et al*, 1993)	Varghese 2009 (Varghese *et al*, 2009)	
			Sekar 2015 (Sekar *et al*, 2015)	Wiedemann 1999 (Wiedemann *et al*, 1999)	
			Sheehan 1997 (Sheehan *et al*, 1997)	Yoshino 1992 (Yoshino *et al*, 1992)	
			Simonian 1993 (Simonian and Hyman, 1993)		
			Simonian 1995 (Simonian and Hyman, 1995)		
			Terni 2010 (Terni *et al*, 2010)		
			Valla 2001 (Valla *et al*, 2001)		
			Valla 2006 (Valla *et al*, 2006)		
			Verwer 2000 (Verwer *et al*, 2000)		
			Vitali 2009 (Vitali *et al*, 2009)		
			Wong-Riley 1997 (Wong-Riley *et al*, 1997)		

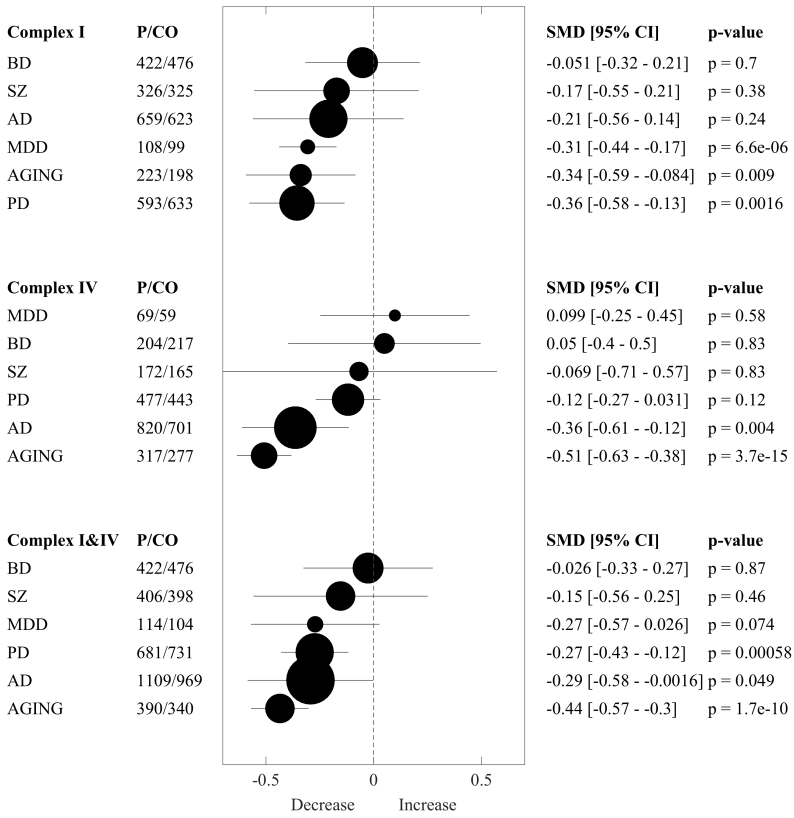
Table 2. (Top) Heterogeneity and Inconsistency. Significant Q statistics indicates the existence of heterogeneity. A I^2 value of 0% indicates no observed inconsistency, whereas larger values shows increasing inconsistency. **(Bottom) Egger's regression test for funnel plot asymmetry.** The existence of funnel plot asymmetry and potential publication bias is indicated by p-values < 0.05. df = degrees of freedom.

Heterogeneity and Inconsistency				
		Q	**p-value**	**I^2 (%)**
MDD	**Complex I**	549.160	0.000	91%
	Complex IV	0.030	1.000	0%
BD	**Complex I**	137410.000	0.000	100%
	Complex IV	873.150	0.000	95%
SZ	**Complex I**	2197.500	0.000	97%
	Complex IV	209.560	0.000	88%
AD	**Complex I**	64812.000	0.000	100%
	Complex IV	4490.300	0.000	97%
PD	**Complex I**	437.650	0.000	80%
	Complex IV	3083.300	0.000	99%
AGING	**Complex I**	27.934	0.218	18%
	Complex IV	11.684	1.000	0%
Egger's regression				
		z-value	**df**	**p-value**
MDD	**Complex I**	-1.969	4	0.120
	Complex IV	0.630	2	0.593
BD	**Complex I**	-2.191	17	0.043
	Complex IV	-0.042	8	0.968
SZ	**Complex I**	0.135	13	0.895
	Complex IV	1.035	8	0.331
AD	**Complex I**	-0.109	17	0.915
	Complex IV	-1.381	37	0.176
PD	**Complex I**	-2.127	30	0.042
	Complex IV	-0.176	26	0.862
AGING	**Complex I**	-1.025	9	0.332
	Complex IV	-2.820	13	0.014



a)	**Complex I**	**MDD/CO**	**SMD [95% CI]**	**p-value**
	NDU muscle	46/30	-0.32 [-0.85 - 0.21]	p = 0.24
	NDUFS1 cerebellum	30/30	-0.67 [-1.2 - -0.18]	p = 0.0075
	NDUFS1 frontal	30/30	-0.18 [-0.62 - 0.26]	p = 0.43
	NDUFS1 striatum	30/30	0.18 [-0.26 - 0.62]	p = 0.42
	NDUFV1 cerebellum	30/30	-0.89 [-1.4 - -0.43]	p = 0.00014
	NDUFV1 frontal	30/30	-0.46 [-0.92 - -0.0068]	p = 0.047
	NDUFV1 parietal	30/30	-0.039 [-0.55 - 0.48]	p = 0.88
	NDUFV1 striatum	30/30	-0.13 [-0.59 - 0.33]	p = 0.58
	NDUFV2 cerebellum	30/30	-0.84 [-1.4 - -0.25]	p = 0.0051
	NDUFV2 frontal	30/30	-0.38 [-0.91 - 0.16]	p = 0.16
	NDUFV2 parietal	30/30	-0.053 [-0.5 - 0.39]	p = 0.81
	NDUFV2 striatum	30/30	-0.13 [-0.58 - 0.33]	p = 0.59
	Complex IV	**MDD/CO**	**SMD [95% CI]**	**p-value**
	COX_{muscle}	17/30	0.26 [-0.33 - 0.85]	p = 0.39
b)	**Complex I**	**BD/CO**	**SMD [95% CI]**	**p-value**
	NDU blood	47/60	-0.099 [-0.34 - 0.14]	p = 0.43
	NDUFS1 blood	68/71	0.042 [-0.41 - 0.49]	p = 0.85
	NDUFS1 cerebellum	30/30	-0.63 [-0.9 - -0.35]	p = 8e-06
	NDUFS1 frontal	30/30	-0.3 [-0.57 - -0.024]	p = 0.033
	NDUFS1 striatum	30/30	-0.36 [-0.59 - -0.13]	p = 0.0023
	NDUFS7 frontal	110/120	-0.37 [-0.51 - -0.23]	p = 1.5e-07
	NDUFV1 blood	68/71	0.14 [-0.27 - 0.56]	p = 0.49
	NDUFV1 cerebellum	30/30	-0.63 [-1.5 - 0.19]	p = 0.13
	NDUFV1 frontal	81/91	-0.16 [-0.34 - 0.029]	p = 0.099
	NDUFV1 parietal	30/30	0.19 [-0.29 - 0.67]	p = 0.44
	NDUFV1 striatum	30/30	-0.048 [-0.37 - 0.28]	p = 0.77
	NDUFV2 blood	179/208	0.088 [-0.18 - 0.36]	p = 0.52
	NDUFV2 cerebellum	30/30	-0.5 [-1.1 - 0.095]	p = 0.099
	NDUFV2 frontal	30/30	-0.055 [-0.32 - 0.21]	p = 0.69
	NDUFV2 parietal	30/30	0.23 [-0.064 - 0.52]	p = 0.13
	NDUFV2 striatum	30/30	-0.042 [-0.3 - 0.22]	p = 0.75
	Complex IV	**BD/CO**	**SMD [95% CI]**	**p-value**
	COX4 blood	21/21	0.016 [-0.17 - 0.21]	p = 0.87
	COX5 blood	34/32	-0.11 [-0.24 - 0.017]	p = 0.087
	COX6 blood	71/57	-0.14 [-0.28 - 0.0018]	p = 0.053
	COX7 blood	71/57	-0.061 [-0.19 - 0.063]	p = 0.34
c)	**Complex I**	**SZ/CO**	**SMD [95% CI]**	**p-value**
	NDU blood	128/125	0.28 [-0.2 - 0.76]	p = 0.25
	NDUFS1 blood	39/37	0.85 [0.35 - 1.3]	p = 0.00086
	NDUFS1 cerebellum	30/30	-0.34 [-0.72 - 0.033]	p = 0.074
	NDUFS1 frontal	30/29	-0.18 [-0.48 - 0.13]	p = 0.26
	NDUFS1 striatum	30/30	-0.58 [-0.92 - -0.25]	p = 0.00072
	NDUFS7 frontal	79/85	-0.17 [-0.38 - 0.034]	p = 0.1
	NDUFV1 cerebellum	30/30	-0.18 [-0.49 - 0.12]	p = 0.24
	NDUFV1 frontal	84/90	-0.5 [-0.88 - -0.12]	p = 0.011
	NDUFV1 parietal	30/29	0.43 [-0.29 - 1.1]	p = 0.24
	NDUFV1 striatum	30/30	-0.87 [-1.2 - -0.57]	p = 1.1e-08
	NDUFV2 blood	40/35	-0.7 [-1.3 - -0.12]	p = 0.019
	NDUFV2 cerebellum	30/30	-0.21 [-0.49 - 0.078]	p = 0.15
	NDUFV2 frontal	30/29	-0.81 [-1.8 - 0.14]	p = 0.096
	NDUFV2 parietal	30/29	0.46 [0.077 - 0.84]	p = 0.019
	NDUFV2 striatum	30/30	-0.82 [-1.2 - -0.45]	p = 1.7e-05
	Complex IV	**SZ/CO**	**SMD [95% CI]**	**p-value**
	COX frontal	35/31	-0.47 [-0.86 - -0.087]	p = 0.016
	COX P/NA/GP	23/26	0.58 [0.34 - 0.83]	p = 2.5e-06
	COX4 substantia nigra	16/13	-0.25 [-0.58 - 0.087]	p = 0.15


a)
Complex I AD/CO SMD [95% CI] p-value
NDU blood 73/92 0.2 [-0.095 - 0.5] p = 0.18
NDU frontal 47/41 0.076 [-0.23 - 0.38] p = 0.62
NDU temporal/entorhinal 101/77 -0.37 [-0.61 - -0.13] p = 0.0023
NDUFA1/4/7-9 blood 104/105 -0.25 [-0.37 - -0.14] p = 1.9e-05
NDUFA2 entorhinal 45/39 0.15 [-0.41 - 0.71] p = 0.59
NDUFA2 frontal 42/36 0.12 [-0.41 - 0.64] p = 0.66
NDUFB2/3/6 blood 104/105 -0.26 [-0.39 - -0.14] p = 1.8e-05
NDUFB3 entorhinal 29/16 0.086 [-0.64 - 0.81] p = 0.82
NDUFB3 frontal 27/16 0.24 [-0.24 - 0.73] p = 0.33
NDUFB7 entorhinal 44/36 0.073 [-0.42 - 0.57] p = 0.77
NDUFB7 frontal 43/39 0.14 [-0.35 - 0.63] p = 0.57
NDUFS3/4/5 blood 104/105 -0.32 [-0.45 - -0.19] p = 1.8e-06
Complex IV AD/CO SMD [95% CI] p-value
COX blood 120/137 -0.36 [-0.79 - 0.074] p = 0.1
COX cerebellum 96/47 -0.11 [-0.55 - 0.32] p = 0.6
COX frontal 211/161 -0.4 [-0.79 - -0.012] p = 0.044
COX hippocampus 198/145 -0.5 [-0.73 - -0.26] p = 2.8e-05
COX motor 86/52 -0.35 [-0.54 - -0.16] p = 0.0003
COX occipital 56/58 -0.31 [-0.6 - -0.026] p = 0.032
COX parietal 121/92 -0.49 [-0.77 - -0.21] p = 0.00069
COX substantia nigra 61/26 -0.18 [-0.53 - 0.17] p = 0.32
COX temporal/entorhinal 190/142 -0.54 [-0.82 - -0.27] p = 0.00012
COX2 hippocampus 16/13 -1.2 [-1.5 - -0.85] p = 1.5e-11
COX7 blood 104/105 -0.27 [-0.47 - -0.061] p = 0.011
COX7 entorhinal 42/27 -0.49 [-1.7 - 0.72] p = 0.43
COX7 frontal 29/16 -0.51 [-1.6 - 0.57] p = 0.36
b)
Complex I PD/CO SMD [95% CI] p-value
NDU blood 230/236 -0.18 [-0.41 - 0.048] p = 0.12
NDU muscle 88/148 -0.4 [-0.64 - -0.17] p = 0.00084
NDU frontal 77/68 -0.37 [-0.91 - 0.17] p = 0.18
NDU substantia nigra 81/84 -0.4 [-0.69 - -0.12] p = 0.006
Complex IV PD/CO SMD [95% CI] p-value
COX blood 217/193 -0.16 [-0.38 - 0.066] p = 0.17
COX muscle 76/90 -0.22 [-0.67 - 0.23] p = 0.34
COX cerebellum 28/30 -0.075 [-0.34 - 0.19] p = 0.58
COX frontal 41/44 -0.39 [-0.76 - -0.025] p = 0.036
COX substantia nigra 32/29 -0.026 [-0.37 - 0.32] p = 0.88
c)
Complex I O/Y SMD [95% CI] p-value
NDU frontal 34/41 -0.45 [-0.67 - -0.23] p = 6.7e-05
NDU muscle 62/60 -0.4 [-0.58 - -0.22] p = 2e-05
NDUFB8 muscle 84/54 -0.41 [-0.62 - -0.2] p = 0.00015
Complex IV O/Y SMD [95% CI] p-value
COX frontal 54/57 -0.57 [-0.98 - -0.15] p = 0.0072
COX muscle 176/165 -0.45 [-0.7 - -0.21] p = 0.00027
COX2 muscle 68/41 -0.53 [-0.78 - -0.28] p = 3.1e-05
-1.5
-1
-0.5
0
0.5
1
Decrease
Increase


Complex I
P/CO
SMD [95% CI]
p-value
BD
422/476
-0.051 [-0.32 - 0.21]
p = 0.7
SZ
326/325
-0.17 [-0.55 - 0.21]
p = 0.38
AD
659/623
-0.21 [-0.56 - 0.14]
p = 0.24
MDD
108/99
-0.31 [-0.44 - -0.17]
p = 6.6e-06
AGING
223/198
-0.34 [-0.59 - -0.084]
p = 0.009
PD
593/633
-0.36 [-0.58 - -0.13]
p = 0.0016
Complex IV
P/CO
SMD [95% CI]
p-value
MDD
69/59
0.099 [-0.25 - 0.45]
p = 0.58
BD
204/217
0.05 [-0.4 - 0.5]
p = 0.83
SZ
172/165
-0.069 [-0.71 - 0.57]
p = 0.83
PD
477/443
-0.12 [-0.27 - 0.031]
p = 0.12
AD
820/701
-0.36 [-0.61 - -0.12]
p = 0.004
AGING
317/277
-0.51 [-0.63 - -0.38]
p = 3.7e-15
Complex I&IV
P/CO
SMD [95% CI]
p-value
BD
422/476
-0.026 [-0.33 - 0.27]
p = 0.87
SZ
406/398
-0.15 [-0.56 - 0.25]
p = 0.46
MDD
114/104
-0.27 [-0.57 - 0.026]
p = 0.074
PD
681/731
-0.27 [-0.43 - -0.12]
p = 0.00058
AD
1109/969
-0.29 [-0.58 - -0.0016]
p = 0.049
AGING
390/340
-0.44 [-0.57 - -0.3]
p = 1.7e-10
-0.5
0
0.5
Decrease
Increase

MDD	• Small number of studies with small sample sizes • Region-specific heterogeneity • **Moderate effects in complex I, small effects in complex IV**
BPD	• Small sample sizes • Region-specific heterogeneity • **Moderate effects in complex I, small effects in complex IV**
SZ	• Small sample sizes • Region-specific heterogeneity • **Moderate effects in complex I and IV**
AD	• Large number of studies with large sample sizes • Tissue-specific heterogeneity (low in blood, high in brain) • **Strong effects in complex I and IV**
PD	• Large number of studies • No heterogeneity • **Strong effects in complex I and IV**
AGING	• Most robust effects • No heterogeneity • **Strongest effects in complex I and IV**